Imperial College Healthcare NHS
NHS Trust

IgM HLA Donor Specific Antibodies Do Not Alter Outcomes of Renal Allograft Rejection

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Background

Well known that IgG HLA DSAs are associated with renal allograft rejection and graft loss

However the role of IgM HLA DSAs is controversial

Study	Year	Outcome
McCalmon	1997	IgM DSAs not associated with hyper-acute rejection
Kerman	1999	IgM may be protective against AMR
Stasney	2009	IgM predicted rejection and TCAD
Everly	2014	IgM in association with IgG3 resulted in higher rates of allograft failure
Babu	2016	IgM de novo DSA associated with graft failure

Paucity of evidence regarding outcomes of transplant recipients with IgM DSA

Background

1. IgM appears first in the humoral response
2. Potent at agglutinating and binding antigen
3. Strong affinity to fix complement
4. Unclear if IgM alloantibodies damage renal allografts directly
5. Used to explain some of the causes of IgG DSA negative AMR
6. Do these antibodies play a role in combination with IgG to create a more severe phenotype of AMR

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Aims of the study

1. Describe the class of IgM DSAs that appear during allograft rejection

2. Compare graft survival of patients with an IgM DSA after confirmed allograft rejection

3. Identify whether IgM alone or together with IgG worsen outcomes of rejection

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Methods

1667 CDC/FXCM negative transplant recipients investigated between June 2005 - August 2016

All patients received monoclonal antibody induction, with a tacrolimus based, steroid sparing maintenance immunosuppressive protocol

Indicative biopsies studies identifying four patient cohorts

1. 50 with T-Cell mediated rejection (TCMR)
2. 50 with acute antibody mediated rejection (acute AMR)
3. 57 with cAMR + transplant glomerulopathy
4. 50 controls with no evidence of rejection on a surveillance biopsy

Controls were unsensitised individuals – DSA/HLA negative at the time of surveillance biopsy

Diagnosis of rejection was based on Banff 2015 criteria

Median follow up was 5.5 years (IQR 3.01-7.82)

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Methods

Sera were tested for class I HLA (A/B/Cw) and class II (DR/DQ) antibodies at the time of allograft dysfunction and diagnostic biopsy using the single antigen Luminex assay.
Each sample was tested using PE IgM conjugating antibody

Mean fluorescence intensity value of >500 was considered positive

Patients cohorts were further split according to IgG and IgM DSA positivity

- IgG-/IgM-
- IgG+/IgM-
- IgG-/IgM+
- IgG+/IgM+ (double positive)

Statistical and graphical analysis: IBM SPSS Statistics ver. 20.0

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Demographics - 1

	aAMR (n= 50)	TCMR (n= 50)	Controls (n= 50)	p-value
Female, n (%)	24 (48.0)	18 (36.0)	6 (12.0)	**<0.001**
Age at Tx, years	51.5 ± 12.2	46.3 ± 12.3	53 ± 8.7	**0.009**
Ethnicity: **Caucasian** **Asian** **Afro-caribbean** **Other**	 19 (38.0) 17 (34.0) 6 (12.0) 8 (16.0)	 26 (52.0) 14 (28.0) 4 (8.0) 6 (12.0)	 35 (70.0) 12 (24.0) 3 (6.0) 0 (0.0)	 0.027
LD, n (%)	21 (42.0)	23 (46.0)	24 (48.0)	0.828
Pre-emptive, n (%)	10 (20.0)	16 (32.0)	21 (42.0)	0.060
HLA-A/B MM	2.4 ± 1.1	2.6 ± 1.1	2.6 ± 1.0	0.632
HLA-DR MM	1.0 ± 0.8	1.0 ± 0.8	1.1 ± 0.8	0.882
Total MM	3.4 ± 1.4	3.7 ± 1.6	3.7 ± 1.4	0.640
Induction, n (%) **Anti-CD52** **Anti-IL-2R**	 46 (92.0) 4 (8.0)	 43 (86.0) 7 (14.0)	 49 (98.0) 1 (2.0)	 0.087
Graft loss, n (%)	21 (42.0)	19 (38.0)	1 (2.0)	**<0.001**

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Demographics - 2

	TG (n= 57)	TCR (n= 50)	Controls (n= 50)	p-value
Female, n (%)	23 (40.4)	18 (36.0)	6 (12.0)	**0.003**
Age at Tx, years	45.3 ± 11.8	46.3 ± 12.3	53.0 ± 8.7	**0.001**
Ethnicity: **Caucasian** **Asian** **Afro-caribbean** **Other**	 30 (52.6) 22 (38.6) 4 (7.0) 1 (1.8)	 26 (52.0) 14 (28.0) 4 (8.0) 6 (12.0)	 35 (70.0) 12 (24.0) 3 (6.0) 0 (0.0)	**0.035**
LD, n (%)	35 (61.4)	23 (46.0)	24 (48.0)	0.217
Pre-emptive, n (%)	11 (19.3)	16 (32.0)	21 (42.0)	0.038
HLA-A/B MM	2.3 ± 1.1	2.6 ± 1.1	2.6 ± 1.0	0.217
HLA-DR MM	1.3 ± 0.7	1.0 ± 0.8	1.1 ± 0.8	0.117
Total MM	3.6 ± 1.6	3.7 ± 1.6	3.7 ± 1.4	0.983
Induction, n (%) **Anti-CD52** **Anti-IL-2R**	 39 (68.4) 18 (31.6)	 43 (86.0) 7 (14.0)	 49 (98.0) 1 (2.0)	**<0.001**
Graft loss, n (%)	39 (68.4)	19 (38.0)	1 (2.0)	**<0.001**

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IgM DSA categories

	Acute AMR	TG	TCR	Controls
IgG- / IgM-	22/50 (44.0)	18/57 (31.6)	36/50 (72.0)	42/50 (84.0)
IgG+ / IgM-	18/50 (36.0) *‡	21/57 (36.8) *‡	9/50 (18.0) *	2/50 (4.0)
IgG- / IgM+	3/50 (6.0)	6/57 (10.5)	3/50 (6.0)	6/50 (12.0)
IgG+ / IgM+	7/50 (14.0) *‡	12/57 (21.1) *‡	2/50 (4.0)	0/50 (0.0)

1. *‡ More IgG DSA in the acute AMR, TG and TCR groups compared to controls **p<0.05**
2. *‡ More “double positives” in patients with both acute AMR and TG compared to controls **p<0.01**
3. 12% of controls had an IgM DSA

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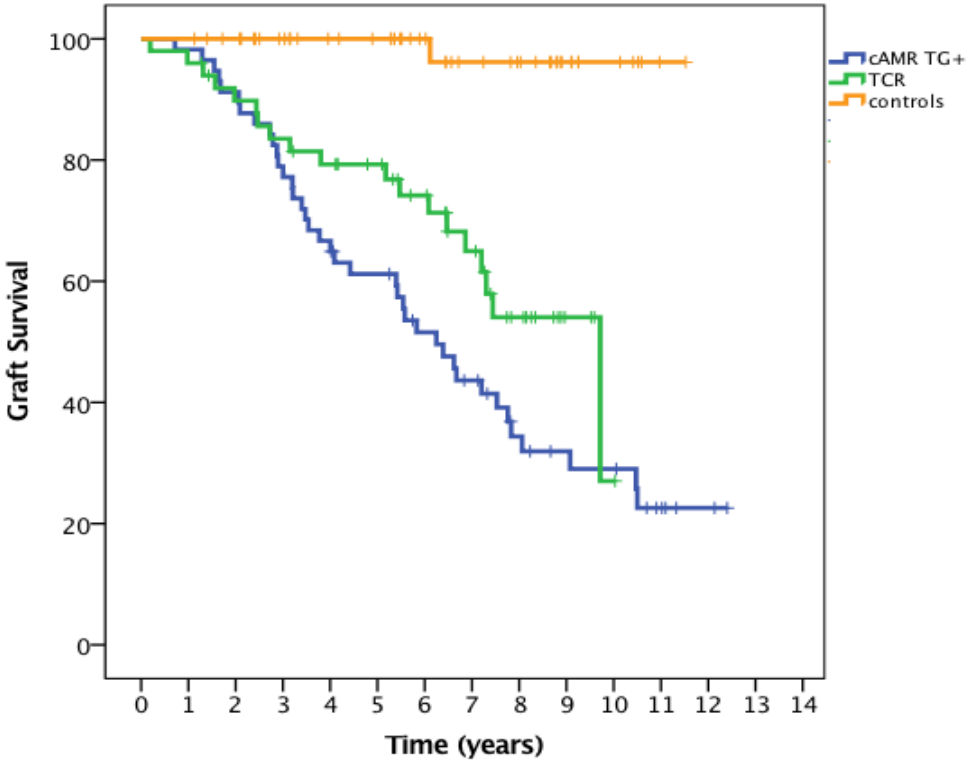
Results – Death Censored Allograft Survival



TG vs TCMR p=0.059, log rank

p<0.001

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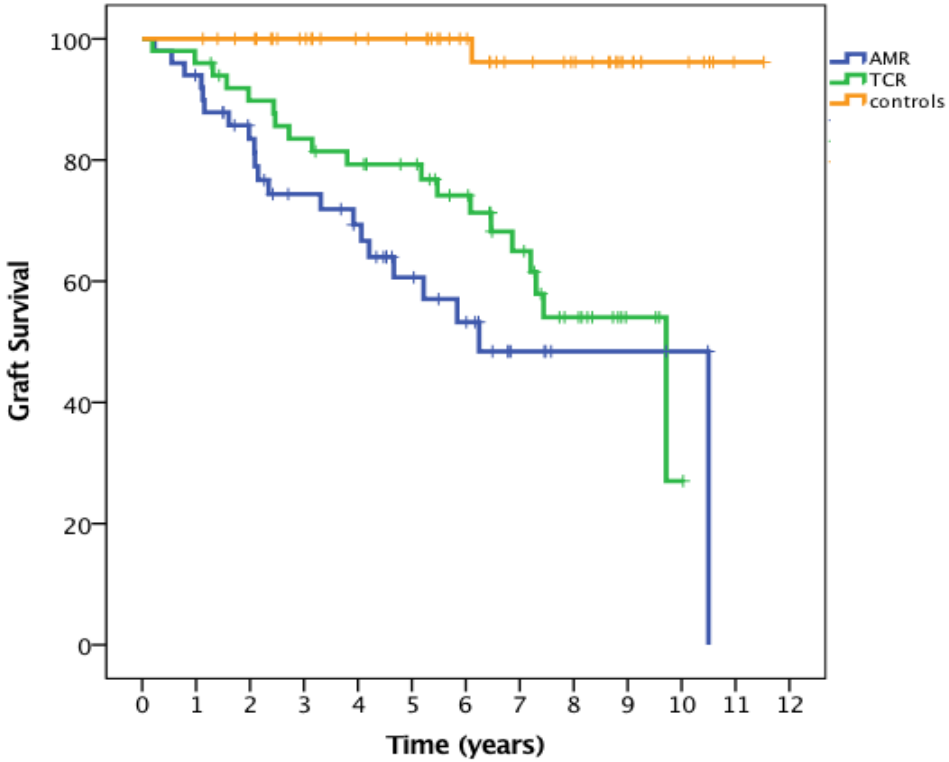
Results – Death Censored Allograft Survival



AMR vs TCR p= 0.206 log Rank

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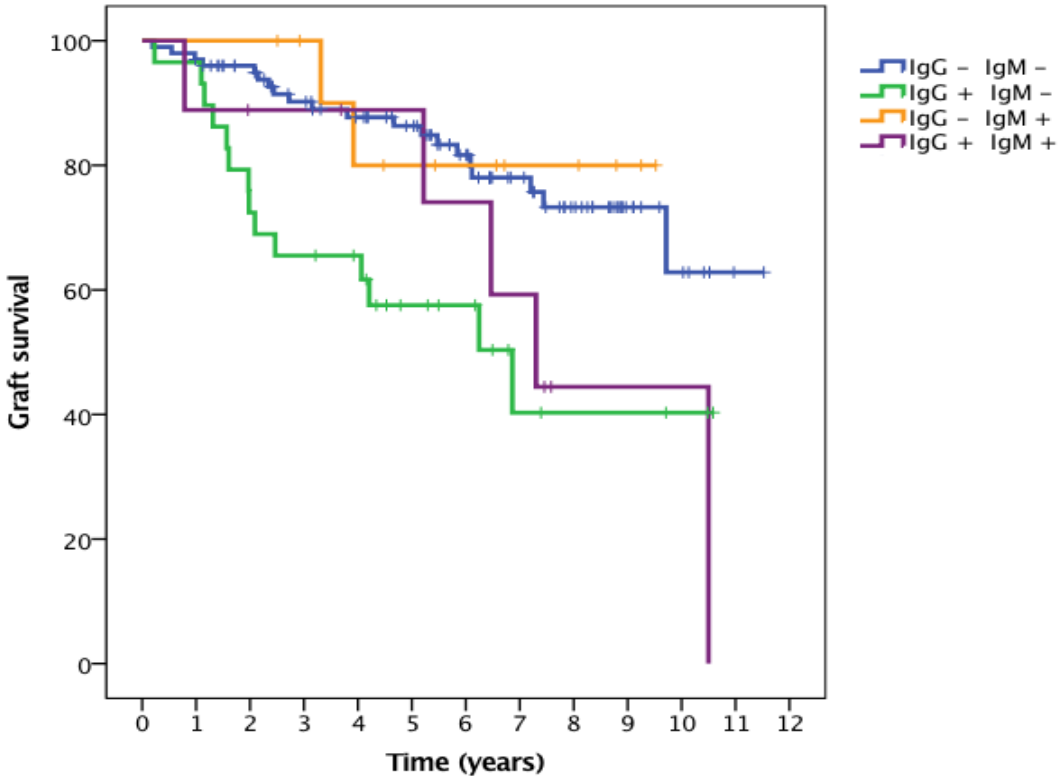
Results – Death Censored Allograft Survival acute AMR/TCR/Controls



IgG-/IgM+ vs IgG+/IgM+

p=0.268

IgG+/IgM+ vs IgG+/IgM-

p=0.688

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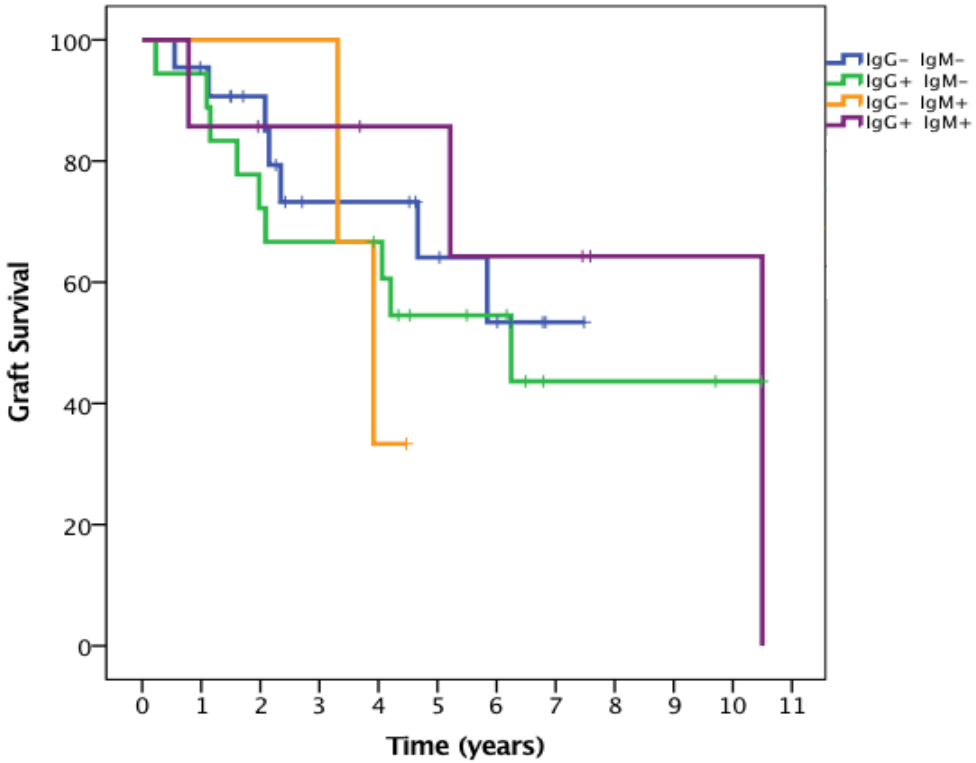
Results – Death Censored Allograft Survival – Acute AMR



p=0.668

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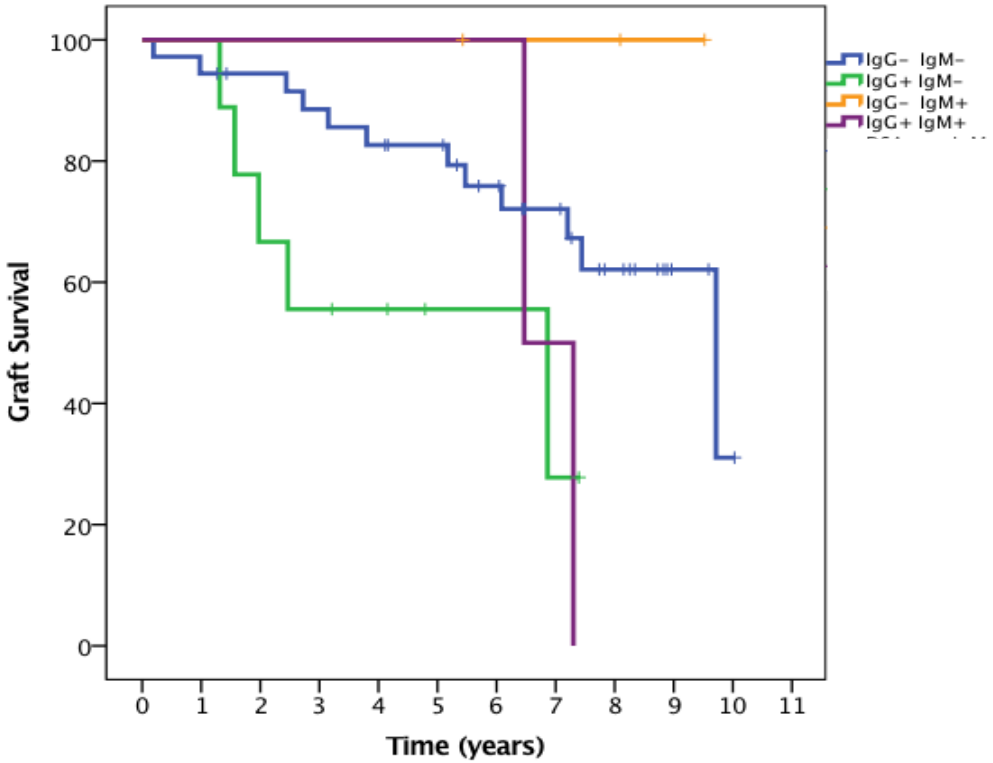
Results – Death Censored Allograft Survival - TCR



p=0.05

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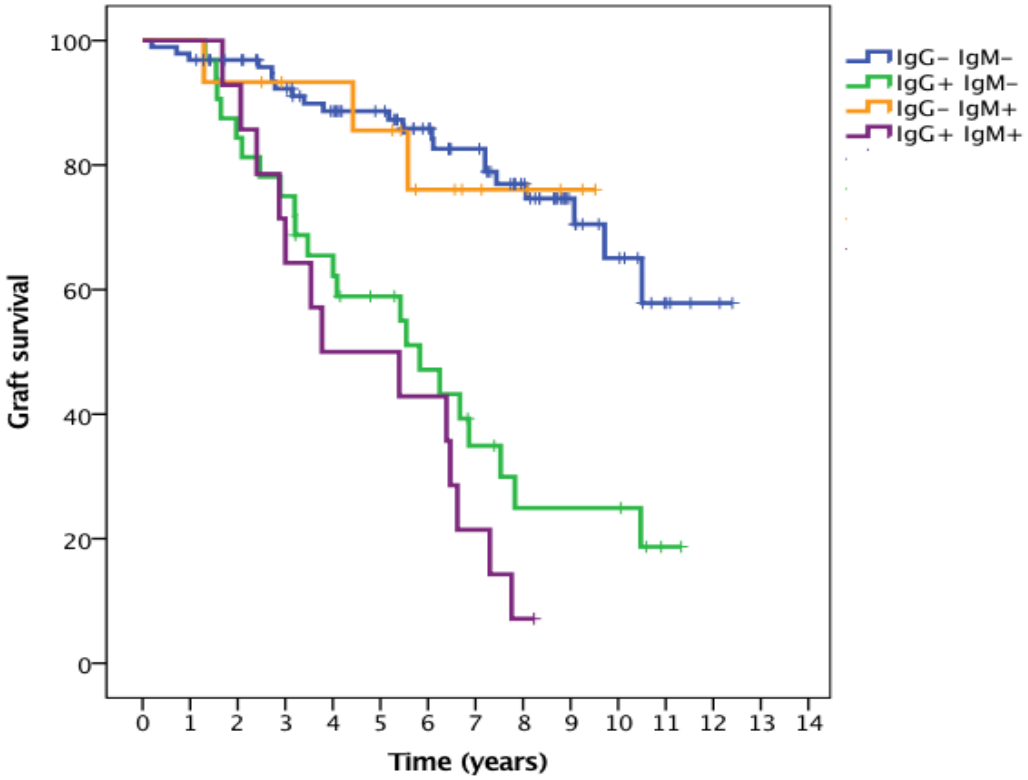
Results – Death Censored Allograft Survival – TG/TCR/Controls



p<0.001

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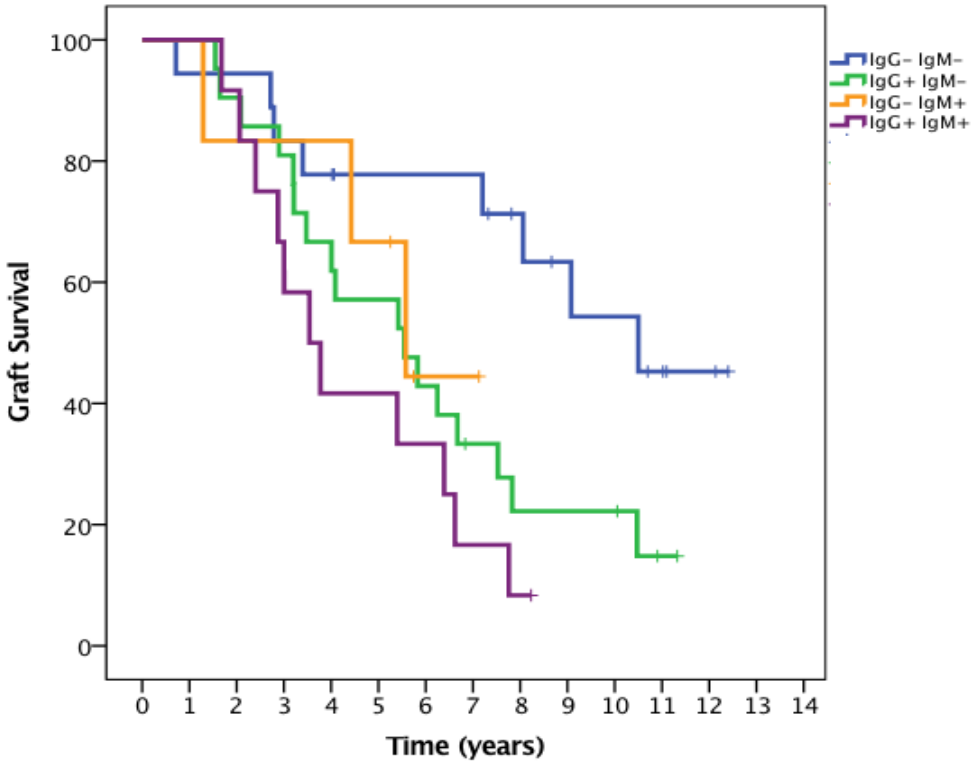
Results – Death Censored Allograft Survival - TG



IgG+/IgM- vs IgG+/IgM+

p=0.231

P= 0.015

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DISCUSSION AND CONCLUSIONS

1. IgM DSAs do not alter outcomes of renal allograft rejection

2. Whilst there is an increased incidence of IgM DSAs in acute and chronic forms of humoral rejection they do not alter outcomes
- Presence of IgM DSA does not alter outcomes in T-cell mediated rejection

3. The presence of an IgM DSA and IgG DSAs does not play a cumulative role to worsen outcomes in any phenotype of allograft rejection

4. IgM may herald a risk of isotype switch to IgG

5. It is the presence of IgG DSA that significantly reduces graft survival in cases of TG positive cAMR

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